REMARKS

Without acquiescing in any rejection, applicants have cancelled, without prejudice or disclaimer, all pending claims 1-13 and 16-29 and replaced these claims with new claims 35-62. Upon entry of this amendment, claims 35-62 will be pending. The new claims correspond to prior claims 1-13 and 16-29 as follows. Claim 4 is now claim 35. Former claims 1, 2 and 3 are now claims 36, 37 and 38, respectively, and are now dependent on claim 35. New claim 36 has also been amended to provide the meaning of "YAC" in full. Method claims 41-47 correspond to former claims 7-13 but are now dependent from or through claim 35. Claim 48 recites expression of an endogenous kappa light chain locus and a human lambda light chain locus, where the expression of the human lambda light chain locus is equal to or greater than that of the endogenous kappa light chain locus. Claim 49 depends from claim 48 and recites expression of a human lambda light chain locus that is equal to or greater than the expression of a human kappa light chain locus. Support for claims 48 and 49 is found in, for example, page 7 of the specification and in originally filed claim 27. New claims 50 and 51, now dependent on claim 48, correspond to former claims 28 and 29, respectively. New claim 52 corresponds to former claim 16, but is now dependent on claim 48. Similarly, new claims 53-62 correspond to former claims 17-26, respectively, with appropriate modification of claim dependency so that they are now dependent on or through claim 48.

The claims are not taught or suggested by the prior art

The amendments to the claims have obviated the grounds of rejections found on pages 2-7 of the office action, where the examiner rejected claims 1-13 and 16-29 as obvious over the Kucherlapati patent in view of Mendez and Popov.

Claim 35 recites a proportion of κ and λ light chains expressed by a transgenic mouse which resembles that found in humans and exhibits relative proportions of ≤60% κ light chains and ≥40% λ light chains. Claim 48 recites expression of an endogenous kappa light chain locus and expression of a human lambda light chain locus that is equal to or greater than the endogenous kappa light chain locus. The remaining new claims depend from either claim 35 or claim 48.

Applicant further submits the affidavit of Professor Maria Africa Gonzalez-Fernandez which attests to non-obviousness and the unexpected properties of the claims over the prior art cited by the Examiner.

Applicant notes that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220

USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43. Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). The references are discussed with these legal concepts in mind.

Neither Popov nor Kucherlapati nor Mendez, either individually or taken together suggest or disclose a mouse (1) expressing a proportion of κ and λ light chains which resembles that found in humans and exhibits relative proportions of $\leq$60% κ light chains and $\geq$40% λ light chains or (2) where the endogenous kappa light chain locus is expressed and the expression of a human lambda light chain locus that is equal to or greater than the endogenous a kappa light chain locus.

In contrast and as explained in the attached affidavit, mice normally produce κ and λ light chains in very different proportions. While 95% of the immunoglobulins in mice carry κ light chains, only 5 % of the antibodies carry λ light chains (see application, page 1, lines 8-9). This low presence of λ light chains is associated with markedly diminished diversity in mice. In contrast to the κ system with multiple V region families, λ light chains in mice will mainly use only one V region (λ1). The present inventor was the first to demonstrate that the introduction of at least a majority of the human Vλ genes of cluster A and all of the human Jλ- Cλ segments into mice completely alters the normal mouse pattern of expression of light chains to the situation that is closer to that found in humans (60 % κ and 40 % λ light chains). This fact is an unexpected finding since it indicates that the human translocus is driving the level of expression of the light chain genes. Moreover, the translocus is changing the pattern of the immunoglobulin repertoire to one resembling the pattern seen in humans. This very important finding was impossible to predict from the design of the transgene alone. This finding makes the transgenic mice attainable according to the invention very useful for generating human antibodies.

The present invention shows high and efficient expression of the translocus in the transgenic mouse. In both Mendez and Kucherlapati, endogenous mouse heavy and κ genes were deleted in the test mice to show expression of transfected human immunoglobulin genes. However, in the transgenic mouse of the present invention, human λ genes could be efficiently expressed even in the presence of the endogenous mouse counterparts, which is the opposite of what was thought to be true according to the art. See application at page 12, lines 20-22. This finding allows for the production

of antibodies comprising high levels of human λ light chains in commercial mice regardless of whether these mice are silenced for endogenous immunoglobulin gene expression, and is considered to be surprising by the skilled person.

The surprising results obtained with the present invention further establish patentability, and the examiner has not demonstrated anything to the contrary. *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); MPEP § 716.02(a). As explained by the Federal Circuit:

> [W]hen an applicant demonstrates *substantially* improved results ... and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.

In re Soni, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphasis in original).

On page 8 of the office action, the examiner alleges that claim 27 reads on a transgenic mouse where the endogenous kappa light chain is disrupted such that the expression of human lamda light chain would necessarily be greater that that of a kappa locus. Without acquiescing in the correctness of this statement, applicants have obviated the rejection by reciting in claim 48 that endogenous kappa locus is expressed and that the expression of a human lambda light chain locus is equal to or greater than the endogenous kappa light chain locus. Applicants submit that one of the advantages of the invention of claim 48 is that the endogenous kappa light chain locus does not need to be disrupted to achieve the desired expression levels.

On page 9 of the office action, the examiner alleges that any expression properties of the 380 Kb YAC of Popov are inherent to the structure of the YAC and

reliance upon this inherency is not improper under *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 82 (CCPA 1975). Applicant respectfully submits that the holding of *In re Skoner* does not support the use of an inherent property to support an obviousness rejection. In the decision of *In re Skoner*, the court held that the examiner's obviousness rejection actually was an anticipation rejection and due to this fact, inherency was a proper grounds of rejection. The decision states in relevant part that:

> Thus, the examiner could only note that the patentees were using identical means (i. e., wire brushing) in an attempt to achieve identical results (i. e., improved adhesion) to those of appellants in order to establish a prima facie case of obviousness. Perhaps the rejection should have been founded upon section 102 instead of section 103. However, this court has sanctioned the practice of nominally basing rejections on section 103 **when, in fact, the actual ground of rejection is that the claims are anticipated by the prior art**. The justification for this sanction is that a lack of novelty in the claimed subject matter, e. g., as evidenced by a complete disclosure of the invention in the prior art, is the "ultimate or epitome of obviousness." [internal citations omitted] Therefore, we agree with the examiner that the extent of abrasion carried out by Baer et al. can be considered inherently the same as that of appellants.

In re Skoner, 517 F.2d at 950 (emphasis added).

As stated in *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966), inherency is not a proper grounds for an obviousness rejection. In the decision of I*n re Spormann*, the court stated that:

> [T]he inherency of an advantage and it's obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is not known.

Id.

On page 9 of the office action, the examiner argues that Mendez teaches that in "xenomouse I" there is an equal distribution of kappa and lambda light chains. Applicant submit, however, that the distribution disclosed in Mendez is between human kappa and mouse lambda. In contrast, the claims recite the relative distribution of human lambda not mouse lambda. Thus, the teaching cited by the examiner does not suggest the instant claims.

For at least these reasons, applicants submit that the person having ordinary skill in the art would not consider the present invention obvious over the disclosures and teachings of Kucherlapati, Mendez and Popov. Accordingly, applicants respectfully request withdrawal of the rejection.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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